UNIVERSITY OF GONDAR

COLLEGE OF MEDICINE AND HEALTH SCIENCES

INSTITUTE OF PUBLIC HEALTH

FREQUENCY OF SEIZURE IN THE LAST 2 MONTHS AND ASSOCIATED FACTORS AMONG PATIENTS WITH EPILEPSY AGED ABOVE 15 YEARS IN UNIVERSITY OF GONDAR REFERRAL HOSPITAL: NEGATIVE BINOMIAL REGRESSION MODEL

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A RESEARCH SUBMITTED TO THE INSTITUTE OF PUBLIC HEALTH, COLLEGE OF MEDICINE AND HEALTH SCIENCES, UNIVERSITY OF GONDAR IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY AND BIOSTATISTICS.

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Abbreviation/Acronym

ACE	Active Convulsive Epilepsy
AED	Anti-Epileptic Drug
AIC	Akakie Information Criteria
BIC	Bayesian Information criteria
HIC	High-Income Countries
HIV	Human Immunodeficiency Virus
ILAE	International League Against Epilepsy
IRR	Incidence Rate Ratio
LIC	Low-Income Countries
ML	Maximum Likelihood
MMAS	Moriskiy Medication Adherence Scale
NBPR	Negative Binomial Poisson Regression
PCA	Principal Component Analysis
PWE	Patient With Epilepsy
Rx	Treatment
UOGRH	University Of Gondar Referral Hospital
UK	United Kingdom
WHO	World Health Organization
ZINB	Zero Inflated Negative Binomial
ZIP	Zero Inflated Poisson

Abstract

Background: About three-fourth of adults with new onset epilepsy become seizure-free with current anti-epileptic drugs, but around one fourth of patients continue to experience seizure which increase the risk of accident, disability, death, and treatment side effects. However, studies in this specific research area are very limited. So, this study addressed the gap in determining the magnitude of number of seizure attack and identifying the factors that provoke repeated seizure in patient with epilepsy.

Objective: To assess seizure frequency in the last 2 months and associated factors among patients with epilepsy aged above 15 years in University of Gondar Referral Hospital, 2017.

Methods: Institution based cross-sectional study was conducted in University of Gondar Referral Hospital. Systematic random sampling was employed to select the 408 study participants. Data was collected by face to face interview using structured questionnaire and analyzed in Stata version 14. Negative Binomial regression model was selected using Log likelihood from Poisson regression.

Results: One third of the study experienced seizure attack with minimum of one and a maximum of seventeen. educational status (college/university (AIRR 0.48 and 95%CI 0.24-0.95), wealth index (middle AIRR 0.65 and 95%CI 0.46-0.91 and rich AIRR 0.55 and 95%CI 0.38-0.8), sleep deprivation AIRR 1.63 and 95%CI 1.14-2.34, adherence(moderate AIRR 0.57 and 95% CI (0.40-0.80) and high AIRR 0.28 and 95% CI (0.19-0.41), duration of treatment(1-5 year (AIRR 0.55 and 95%CI 0.35-0.86), flickering light (AIRR 1.57 and 95% CI (1.13-2.16))and noise(AIRR 1.70 and 95% CI (1.26-2.29) were statistically significant seizure provoking factors.

Conclusion and Recommendation: The number of seizure attack in the last two months found to be higher than the expected seizure frequency which is zero. Health information dissemination for patient with epilepsy about the importance of adherence, common seizure provoking factors and control mechanism would be important for effective control of seizure attack.

Key words: epileptic seizure frequency Gondar Negative Binomial Regression model

1. Introduction

1 .1 Statement of the Problem

Epilepsy is one of the common chronic neurologic disorders characterized by recurrent seizure which is a brief period of uncontrolled involuntary shaking. It may be partial, involving only one part of the body, or generalized, involving the entire body, and they may be accompanied by loss of consciousness and loss of control of bowel or bladder function. In some case it is unclassified. Patient with epilepsy may continue to experience any of the above types of seizure while getting antiepileptic drugs (AEDs) treatment(1, 2).Partial seizure also further classified as partial with secondary generalization if a clinical description of an antecedent symptom (aura), or a clear electroencephalographic signature of focality is indicated, whereas generalized seizure(generalized onset seizure) type include absence, tonic, clonic, tonic-clonic, myoclonic and atonic(2).

Epilepsy accounts one percent for the global burden of disease. In 2008 globally there were 50 million patients with epilepsy; of whom 40 million are estimated to live in developing countries and among those patients 90% of them do not receive appropriate treatment for their problem. In 2010 more than 62 million epileptic people live in low and middle -income countries(3, 4).

Epilepsy can be diagnosed and treated inexpensively. Patients with epilepsy have poor health outcomes, including greater psychological distress, depression, anxiety, employment restriction, more physical injuries such as fractures and burns, and increased mortality, besides epileptic seizures result in devastating social consequences which result in poor quality of life(1). Seizure frequency is a significant factor for depression which is among the leading causes of disability. When the number of seizure frequency increases a patient probability of developing perceived stigma also increase which further results in the devastating social consequences and complicate patient quality of life(5).

A retrospective study conducted in Ethiopia on 119 epileptic patients(status epilepticus) showed that from the total study participants 58% of the patients who develop

generalized tonic-clonic seizure at baseline evaluation with the frequency of ≤8 times, 23.2% of them died , from 16 of patient with 9-12 seizure at baseline 13.4% of them died, there is no history of death among 4.2% of participants with >13 seizure and among 24.4% of participant with unknown history of seizure frequency 10.3% were died due to a number of factors but CNS infection and non-compliance with ADE accounts 43% and 21% respectively(6). A community-based study in rural Ethiopia also showed that 20 of the 316 persons with epilepsy (6.3%) died over a 2-year period, most deaths occurred due to status epilepticus and burn(7).

The Federal Ministry of Health in Ethiopia has recently issued a Mental Health Strategy that aims to develop mental health services that are “decentralized and integrated at the primary health care level(8). The general objective of the strategy is to provide quality mental health services to the people of Ethiopia that are accessible, free or affordable, equitable, efficient and effective, through the integration of mental health into primary health care, while focusing on priority disorders and vulnerable groups(9).

1.2 Literature Review

1.2.1 Frequency of seizure among patients with epilepsy

A seizure is a clinical hallmark of epilepsy. About 70-80% of adults with new onset epilepsy will become seizure-free with current antiepileptic drugs, but around 20-30% of patient will continue to experience seizures with available anti-epileptic drugs which have a significantly increases risk of accident, disability, death, and adverse effects from antiepileptic drugs(10).

A systematic review conducted on 160 countries showed that the prevalence of epilepsy in Africa is 11.29 per 1000 population, estimated population affected by epilepsy is around 3, 367,000 individuals this is 26% higher than the worldwide mean prevalence of epilepsy which was 8.93 per 1000 population(11).

A study conducted in USA on seizure reduction and quality of life found that from a total of 134 subjects who experienced a reduction in seizure frequency, 16% became seizure free, 13% had a reduction in seizure frequency by 75–94%, and 25% of them experienced reduction by 50–74%. Less than a 50% increase or decrease in seizure frequency was observed in 46% of the participant. From the observed seizure about 51.6% seizure type are complex partial 26.2%, tonic–clonic and 21.7% both(12).

A study conducted in UK on seizure frequency and severity showed that from a total of 1630 participants 51.7% of the patients have no seizure, but one seizure in 7.9%, 2-9 seizure in 17.2%, 10-99 seizure in 17.4% and 5.8% of them were experienced 100 seizure for the last twelve month(13). A prospective follow-up study in Scotland done on 525(470 new and 55 on antiepileptic drug) participant showed that the number of seizure at baseline were one seizure in 21 participants, 2 seizures in 80, 3-5 seizures in 109, 6-10seizures in 73, 11-20seizures in 57 and > 20 seizures in 185 participants. During follow- up from 470 new patients 64% of the participants became seizure free with mono therapy of antiepileptic drug(14).

A study finding in India on perceived triggering factor of seizure in a person with epilepsy indicates the number of seizure frequency per month among a total of 405

patients with epilepsy the frequency of seizure in 53.8% is ≤ 2 per month and >2 attack per month in 46.2% of the patient(15).

A study conducted in Italy showed that from the total of 104 study participants 8% of them experience seizure daily, 24% of them weekly, 28% of them monthly, 43% of them yearly and 25% of them became seizure free for more than one year (16).

According to WHO in Africa, the annual incidence of epilepsy is two times higher than in the developed countries. The increased burden of epilepsy in developing country may be related to poor health care services and increased incidence of risk factors such as CNS infections(17).

A cross-sectional study conducted in Nigeria stated that from a total of 89 study participants frequency of seizure attack were ≤4 seizures/year in 37.1% of patients, 32.5% patients had between 5-12 attacks/year and 30.3% patients had >12 attacks/year. However, the sample size for the study was small(18). A cross-sectional study conducted in Egypt on 90 patients with epilepsy showed that about 55 epileptic patients with a history of recent breakthrough seizures were asked the number of seizure in the last year and about 70.9% respond less than one seizure, 27.3% of them experience 1-2 seizure and 1.8% of the participant experience greater than 2 seizure per year(19). A cross-sectional observational study in Nigeria revealed that the level of seizure control in terms of the number of seizure attack per year so from the total of 90 study participant 37% of the study subject have got ≤4 attack/year, 5-12attack/year in 31.5% and ≥12 attack/year in 31.5%(18).

A study conducted in Yirgalem hospital showed that around half (48.5%) of the participants responded that their seizure is not controlled with taking an antiepileptic drug which is a majority of the participant were on Phenobarbital and Carbamazepine this result may be due to non-adherence to treatment(20). A cross-sectional study conducted in Gondar Hospital showed that the number of seizure per year as a factor of perceived stigma is from a total of 408 study participants 85 of them was seizure free, 293 of the participants experience 1-11 seizure per year and 30 of them experience ≥1 seizure per month(5).The main medication for the treatment of active epilepsy in Ethiopia is Phenobarbital 80%, Phenytoin 10% Carbamazepine 5% and

Sodium valproate 5%. In Ethiopia, only 5% of patients with epilepsy receive medical treatment. Even if appropriate treatment successfully controls most cases and leads to remission in at least 70% of patient. So, consistent epilepsy treatment is needed to prevent the recurrence of seizures(21).

1.2.2 Factors associated with seizure attack among patients with epilepsy

Socio-economic factors

According to international league against epilepsy, the risk factors of epilepsy are broadly classified into idiopathic, symptomatic, and cryptogenic. Different studies show that patient socio-demographic statuses are significant factors for epilepsy and/or seizure frequency which include age, sex (2, 7, 22). However, a cross-sectional study conducted in Uganda revealed that factors like age, sex, marital status and level of education are not significant(23). According to a cross-sectional study on large sample size showed that active epilepsy is higher among people with low educational status(24). Participants place of residence can be a risk factor for seizure frequency however, there is no significant difference in seizure triggering factor among female and male(18).

Behavioral factors

Psychoactive substance can change the brain activity. The behavior and lifestyle are important predictors of individual health, especially for chronic diseases. Alcohol consumption can provoke seizure and exacerbate primary epilepsy(7). Smoking, alcohol, sleep deprivation and heavy physical activity found to be a significant triggering factor for seizure in patients with epilepsy (15).

Environmental factors

Environment plays a great role in the development of different diseases. A seizure can be triggered by a number of environmental factors like high humidity, noise, and flickering light(Television) and weather change which can increase or decrease seizure frequency(15).

Clinical factors

In developing countries like Ethiopia infection (bacterial, viral and parasitic) is the common factor for provoking seizure in patients with epilepsy (7, 22, 23). In addition to infection head injury also significantly associated with epileptic seizure(7, 22). Fever

and pain are a significant triggering factors for seizure among patients with epilepsy (15).

The etiologies of epilepsy in developing countries are considerable and most of the factors are preventable factors. Some of the risk factors include infection, head trauma, cerebral infections, psychiatric problems, tumors cerebral infarctions and perinatal accident. Non-communicable diseases like stroke and other vascular diseases and misuse of illicit drugs are also among the common risk factors, especially in high-income countries. These factors may vary in low and high-income countries (7, 11, 22, 24, 25).

Treatment-related factors

Seizure frequency expected to decrease with the administration of antiepileptic drugs with the right dose and duration. A systematic review suggested that a dramatic difference in the care and treatment of epilepsy and difference in treatment gap between high-income countries (HIC) and low-income countries (LIC) and within country which is directly related to seizure frequency(26).

Taking prescribed medication according to prescription can effectively control the disease progression and promote healing. A study conducted in India, Egypt and Uganda shows that missing doses of medication (adherence to treatment) and duration of epilepsy are a significant predictor of seizure(15, 23). Whereas other study stated that there is no significant difference between the duration of epilepsy and type of seizure. Number of AED is a significant factor for seizure frequency(19). low socio-economic status which may be reason for forgetting refill of AED and non-adherence to antiepileptic medication also factors for seizure frequency(27).

The estimated risk of seizure frequency among high-risk patients with epilepsy varies with time of initiation of treatment and the probability also increases with the duration of treatment. A randomized controlled trial shows that seizure free period declines with successive drug regimens, most markedly from the first to the third antiepileptic drug(10).

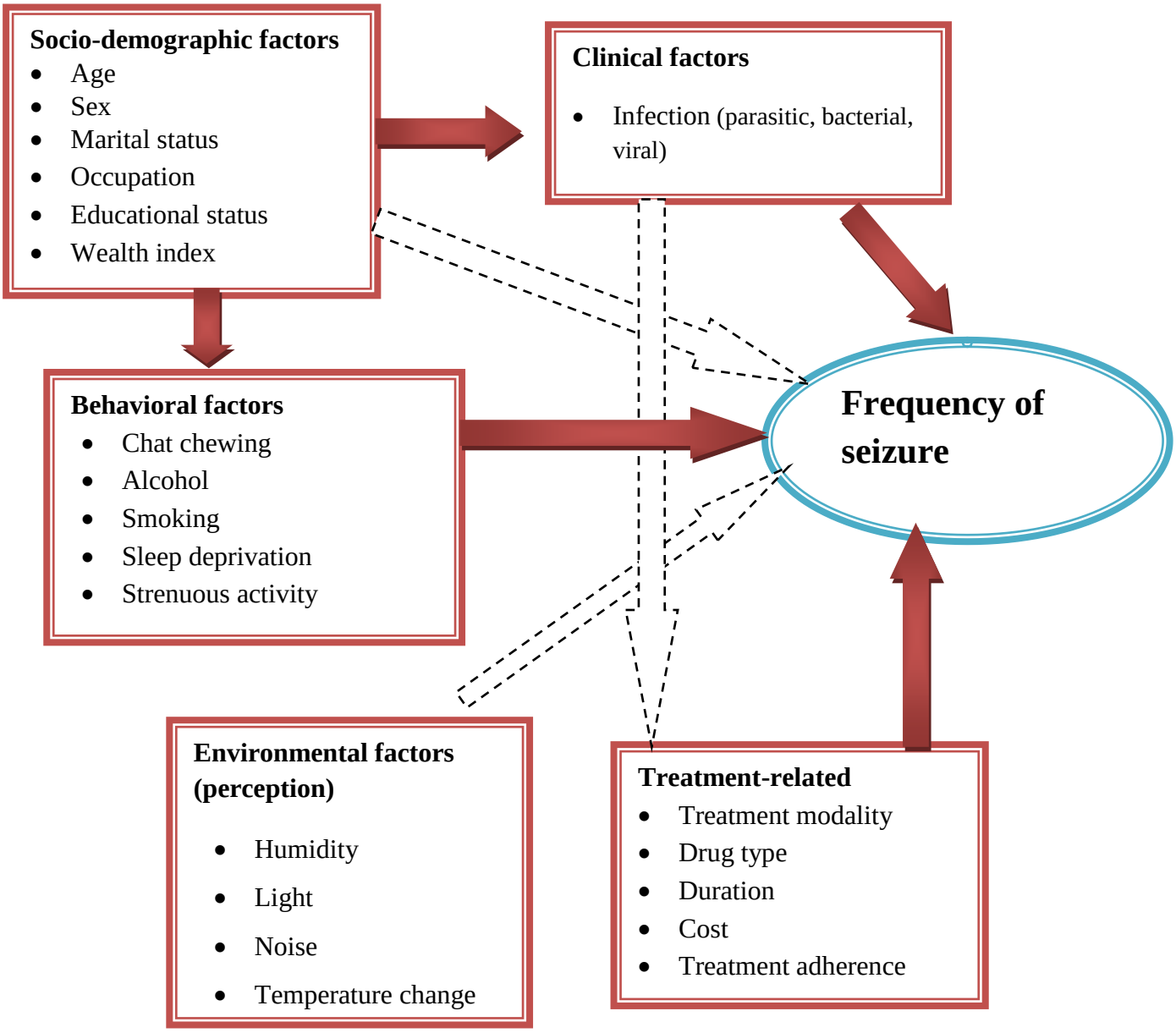

Figure 1 Conceptual framework for seizure frequency and associated factors among patient with epilepsy aged above 15 years in University of Gondar Referral hospital, 2017.

Adopted from (1, 11, 12, 14, 21-24, 28)

1.3 Justification of the study

In Ethiopia, the main focus of health service has been on the prevention, management and control of communicable diseases. Epilepsy is a public health problem characterized by a recurrent seizure which puts the patient at a higher risk of disability and even death. Studies in this research area are very limited in determining the magnitude and identifying factors that provoke seizure attack. So, this study addressed the gap by determining the magnitude and identified seizure provoking factors that provoke repeated seizure in patients with epilepsy. Besides the research gap, this study employed an advance statistical model for better estimation of seizure frequency and associated factors.

This study has an implication which may influence patients for prevention and control of seizure attack, the health professionals for effective care delivery and decision makers for further attention to the problem and program consideration.

2. Objective

2.1 General objective

To assess seizure frequency in the last 2 months and associated factors among patients with epilepsy aged above 15 years in University of Gondar Referral Hospital, 2017.

2.2 Specific objectives

To determine seizure frequency among patients with epilepsy aged above 15 years in the last 2 months in University of Gondar Referral Hospital, 2017.

To identify factors associated with frequency of seizure attack among patients with epilepsy aged above 15 years in the last 2 months in University of Gondar Referral Hospital, 2017.

3. Methods

3 .1 Study design and period

Institution based cross-sectional study was conducted from March to May 2017.

3.2 Study area

The study was conducted in University of Gondar referral hospital, Gondar, Amhara Region, Ethiopia. UOGRH is located in North Gondar administrative zone, Amhara National Regional state, which is located 750 km Northwest of Addis Ababa (the capital city of Ethiopia). According to 2015 Federal Democratic Republic of Ethiopia Central Statistical Agency population projection major cities of Ethiopia, the total population of Gondar town was estimated to be 323,900 Currently Gondar town has one Referral Hospital (UOGRH), 8 Health Centers, and 14 health post which is government owned; There is also one general Hospital, 13 specialty clinics, 15 medium clinics, and ten primary clinics run by private sectors. The newly constructed UOGRH is 1,000 beds hospital which is believed to serve over five million people in Gondar town and its environs or catchment area. It has been serving the community since 1954. It has a range of specialties including Pediatrics, surgery, Gynecology, psychiatry, HIV care and an outpatient's clinic. The hospital has more than 700 health professionals. The average number of patients with epilepsy who has followed in UOGRH per month is 396.

3.3 Population

3.3.1 Source population

The source population for this study was all patients with epilepsy aged above 15 years and who have follow up in University of Gondar Referral Hospital.

3.3.2 Study population

The study population for this study was patients with epilepsy aged above 15 years and who came for follow up during data collection period and who have been taking anti epileptic drug at least for the last two months in University of Gondar Referral Hospital.

3.4 Inclusion and exclusion criteria

3.4.1 Inclusion

Patients with epilepsy aged above 15 years and who have been taking antiepileptic treatment at least for the last two months was included.

3.4.2 Exclusion

Patients who are unable to communicate were excluded from the study.

3.5 Sample size determination and sampling procedure

There is no previously done study on the number of seizure attack (frequency) so that a number of parameters which are important inputs for sample size determination were not available. Pilot study was conducted before the actual data collection. However, no significant variables were found. To use maximum sample size for the validity of this study considering modified Whitemore (1981) and Signori (1991) proposed methods for normalized Poisson became an option. Using the above simulation approach the calculated sample size for this study was estimated to be 389 with 95%CI and 90% power(28). The final sample size including 5% non-response rate became 408 epileptic patients.

Systematic random sampling was employed to select the eligible study participants. The total patients with epilepsy who have been visiting the hospital per month were checked for the past 6 months and the average number of patients per month became 396. The total population during data collection period became 396*2=792 the interval K is the total population divided by the sample size so, the interval K= 792/408= 2. The first study participant was selected using lottery method and data was collected from every 2nd of patients with epilepsy.

3.6 Variables

3.6.1 Dependent variable

Seizure frequency

3.6.2 Independent variables

Socio-demographic and economic factors: age, sex, marital status, educational status, occupation, and wealth index.

Clinical factors: Infection (viral, bacterial and parasitic)

Treatment-related factors: duration, cost, drug type, treatment modality and adherence.

Behavioral factors: smoking, chat chewing, alcohol consumption, missing meal, sleeping hours, common emotional disturbance (anger, worry, anxiety and frustration) and strenuous activity.

Environmental factors: humidity, noise, flickering light and temprature change.

3.7 Operational definition

Epileptic seizure frequency/number of seizure attack: The number of uncontrolled involuntary shaking involving only one part of the body, or involving the entire body in the last two months.

Wealth index: Categorized based on the principal component analysis (PCA) in to three groups as poor, middle and rich.

Adherence: The degree of agreement between the patient`s behavior with respect to taking the antiepileptic drugs and the recommendation by the clinician as measured by Morisky Medication Adherence Scale as, Low adherence (MMAS < 6), Moderate adherence (6 ≤ MMAS < 8) and High adherence (MMAS = 8).

Behavioral factors: Respondents who have been drinking alcohol, chewing khat and smoking cigarette in the last two months irrespective of frequency and amount are grouped as alcohol consumer, chat chewer and smoker respectively.

Seizure provoking/precipitating factors: Factors that can increase the number of seizure attack in patient with epilepsy.

3.8 Data collection procedure and instrument

Data were collected mainly through face to face interview using structured questionnaire and medical chart review by seven Bsc nurses who are working in the hospital after getting training about the tool and data collection procedure. The questionnaire contains different components which include socio-demographic and economic factors, behavioral factors, clinical factors, environmental factors, and treatment-related factors, and seizure-related factors, MMAS and wealth index questions.

3.9 Data quality control

Structured questionnaires was prepared in English and translated to Amharic and finally after data collection to check the consistency of the tool the Amharic version was translate into English. Translation was done by language experts. The questionnaire was carefully evaluated and pre-tested on 5% of the sample size which became 21 patients with epilepsy at Tseda Health Center prior to the actual data collection. Before data collection, two-day training about the tool and data collection procedure was given to the data collectors and supervisors. The data were collected by trained data collectors. In addition to principal investigator, there were two supervisors who are responsible for monitoring the data collection process. Before data entry, the collected data was carefully examined for completeness by the principal investigator.

3.10 Data processing and analysis

The collected data was cleaned and entered into Epiinfo version 7 and exported to STATA version 14 for further analysis. Descriptive and summary statistics were carried out and presented using graphs and tables. Both bivariable and multivariable analysis were performed to determine the association between seizure frequency and explanatory variables using Negative Binomial Regression model. Variables with a p-value <0.2 in the bivariable analysis were selected for multivariable analysis. Finally, 95% CI of AIRR were presented and interpreted accordingly.

3.11 Ethical consideration

Ethical clearance was obtained from University of Gondar institutional ethical review committee. A formal letter was obtained to communicate with Gondar Referral Hospital and finally, permission letter was obtained to communicate with the department focal person.

The purpose of the study, data collection tool and procedure, including their right to withdraw from the study if they are not comfortable with the instrument or the procedure was explained. Confidentiality was ensured by avoiding recording of personal identifiers, by handling information using codes, passwords and limiting accessibility of the information by other people other than the research team. After providing information about the study objective and procedure verbal and written informed consent and assent was obtained from the study participants.

4. Results

A total of 408 respondents aged 15-80 years were interviewed and the overall response rate of the respondents was 100%. The mean age of the respondents was 29 years with standard deviation (SD) of 13.8 and majority of the respondents 175(42.9%) were between 15-24 years. Around 243(59.5%) of the respondents are male and majority 247(60.5%) of them were from urban residence. The marital status of respondents' shows about 233(57.1%) of them were single. Only 53(13%) of the respondents have an educational status of college and university. Regarding their occupation around 133(32.6%) of the respondents are student.

Table 1 Socio-demographic and economic characteristics of the study participants of seizure frequency and associated factors among patient with epilepsy aged above 15 year in University of Gondar Referral Hospital, 2017(n=408)

Variables	Frequency	Percentage (%)
Age		
15-24	175	42.89
25-34	123	30.15
35-44	49	12.01
45-54	24	5.88
55-64	25	6.13
65-80	12	2.94
Sex		
Male	243	59.56
Female	165	40.44
Residence		
Urban	247	60.54
Rural	161	39.46
Marital status		
Single	233	57.11
Married	138	33.82
Divorced	26	6.37
Widowed	11	2.70

Educational level		
No formal education	158	38.72
Primary	118	28.91
Secondary	79	19.36
Higher	53	13.00
Occupation		
Student	133	32.60
Farmer	111	27.21
Merchant	33	8.09
Employee	45	11.03
Housewife	50	12.25
Other	36	8.82
Wealth index		
Poor	153	37.50
Middle	146	35.78
Rich	109	26.72

Occupation (other): daily labor, pensioner, entreaty

Treatment related result

The common antiepileptic drug used to treat epilepsy is Phenobarbital and from the current medication of the respondents Phenobarbital reported by 253 respondents which accounts for 62.5% of current treatment and mono treatment modality accounts around 75.5%. Anti-epileptic treatment is affordable for 63.5% of the respondents but, from the total of 408 study participants 9.31% of the respondents complain treatment related side effects. On the basis of MMAS 24.57% of the respondents had low adherence and 44.23% of them had high adherence for anti-epileptic drug.

Table 2 Treatment related characteristics of the study participants in seizure frequency and associated factors among patient with epilepsy aged above 15 year in University of Gondar Referral Hospital, 2017(n=408)

Variables	Frequency	Percentage (%)
Type of drug when treatment started		
Phenobarbital	255	62.50
Phentoyin	55	13.48
Carbamazepine	15	3.68
Two or more drugs	79	19.36
Other	4	0.98
Adherence		
Low	100	24.57
Moderate	127	31.20
High	180	44.23
Duration of treatment		
<1 year	52	12.75
1-5year	204	50.00
5-10 year	98	24.02
> 10 year	54	13.23
Treatment modality		
Mono	308	75.49
Poly	100	24.51
Current medication		
Phenobarbital	253	62.01
Phentoyin	31	7.60
Carbamazepine	13	3.19
Two or more drugs	106	25.98
Other	5	1.22
Tapering in the last two month		
Yes	21	5.15
No	387	94.85

Treatment Side effect		
Yes	38	9.31
No	370	90.69
Treatment affordability		
Yes	259	63.48
No	149	36.52

Other: Lamotrigine, Sodium valporate and Haloperidol

Behavior related result

Different behavioral factors were asked and about 47(11.5%) of them were engaged in strenuous exercise and around 73(17.9%) of the study participants reported that they suffered by sleep deprivation in the last two months. Majority 327(80.15%) of the respondents do not eat their meal on time.

Table 3 Frequency of behavioral factors reported by the study participants of seizure frequency and associated factors among patient with epilepsy aged above 15 year in University of Gondar Referral Hospital, 2017(n=408)

Variables	Frequency	Percentage (%)
Smoking		
Yes	4	0.98
No	404	99.02
Alcohol		
Yes	77	18.87
No	331	81.13
Chat		
Yes	8	1.96
No	400	98.04
Strenuous exercise		
Yes	47	11.52
No	361	88.48
Sleep deprivation		
Yes	73	17.89
No	335	82.11

Meal on time		
Yes	81	19.85
No	327	80.15

Common emotional response to stressors

Respondents' emotional responses to self perceived stressors were asked and anxiety and anger holds the first and the second place which accounts 14.95% and 10.29% respectively.

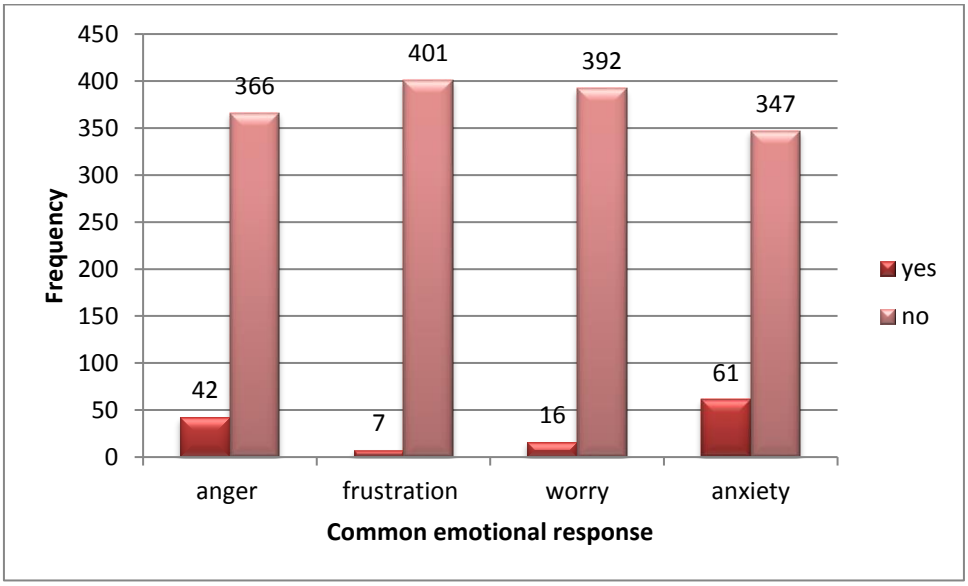

Figure 2 Frequency of common emotional response reported by the study participants of seizure frequency and associated factors among patient with epilepsy aged above 15 year in University of Gondar Referral Hospital, 2017(n=408)

Environment related results

Respondent's perception regarding environmental factors and seizure attack were asked and about 4.6% of them reported as humidity provoke seizure attack. Around 21.5%, 38.7% and 9.07% of the respondents reported to light, noise and weather change respectively.

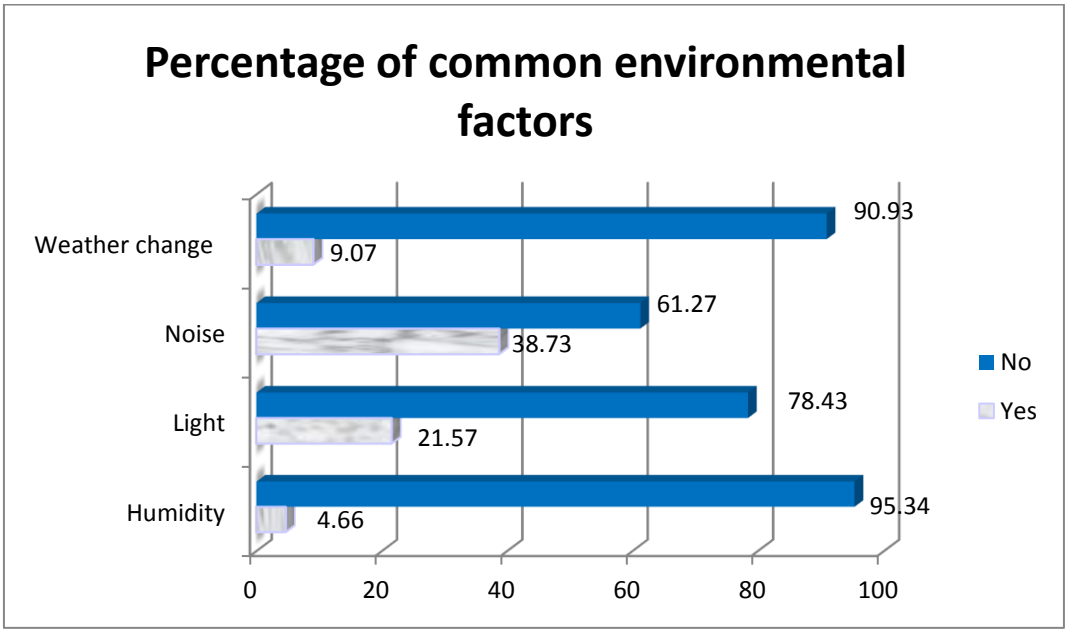

Figure 3 Percentage of self perceived environmental factors reported by the study participants of seizure frequency and associated factors among patient with epilepsy aged above 15 year in University of Gondar Referral Hospital, 2017.(n=408)

Number of seizure attack

The minimum and the maximum seizure attack in the last two months is 0 and 17 respectively. About 59.3% of the respondents reported zero count of seizure attack and only one (0.25%) respondent reported 17 seizure attacks. About 14.2% and 13.4% of them experienced 1 and 2 seizure attack respectively.

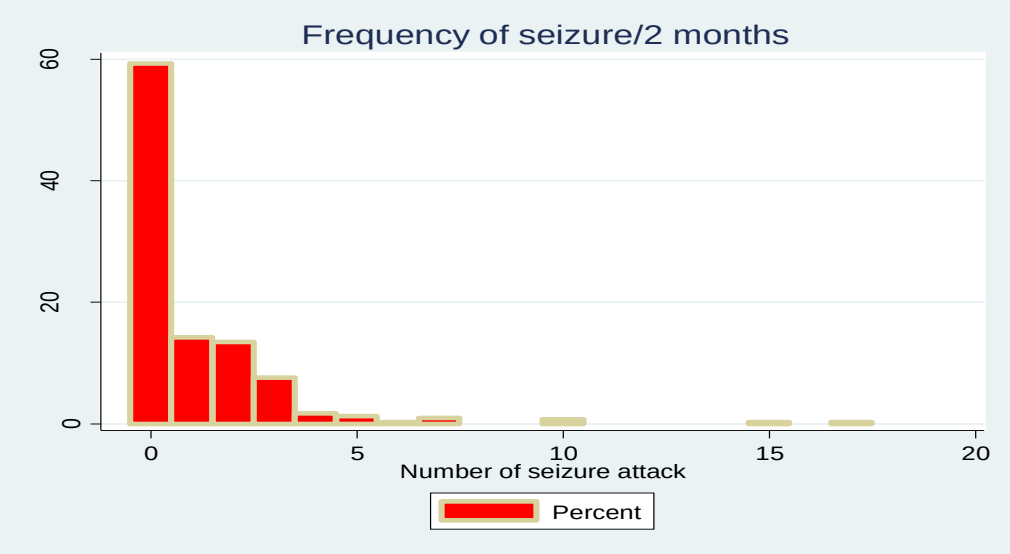

Figure 4 Number of seizure attack in the last two months among study participants of seizure frequency and associated factors among patients with epilepsy aged above 15 years in University of Gondar Referral Hospital, 2017. (n=408)

Clinical factors and seizure frequency

From a total of study participant 27 of them were treated for Acute febrile illness in the last two months among them 15 of them experience seizure attack and 10/408 of study participants who were treated for parasitic infection 5 of them experience seizure attack.

Table 4 Seizure frequencies in the last two months and infection in the study participants of seizure frequency and associated factors among patient with epilepsy aged above 15 year in University of Gondar Referral Hospital, 2017.

Seizure frequency		0	1	2	3	4	5	6	7	10	15	17	Total
AFI	Yes	12	5	3	6	0	0	0	0	0	0	1	27
	No	230	53	52	25	7	5	1	4	3	1	0	381
Parasitic infection	Yes	5	1	2	1	1	0	0	0	0	0	0	10
	no	237	57	53	30	6	5	1	4	3	1	1	398

Factor associated with seizure frequency

The benchmark model for count data is Poisson regression model which assume the mean is equal to variance but for this particular type of data this assumption is violated which is the mean and the variance is 1.004 and 3.5 respectively which is called over dispersion. In order to estimate the over dispersion again to test the significance of over dispersion direct extension of Poisson model was used which is Negative Binomial Poisson regression model which has additional parameter alpha (α). From the model output α value= 0.54 with 95%CI (0.31-0.92) showing significant over dispersion. So, regarding the number of zero count Zero Inflated Negative Binomial (ZINB) model was considered to check the significance of zero count which is around 59.3%. The model output of ZINB model particularly vuong test shows a non significant positive value of 1.39 which favor Negative Binomial Regression model over ZINB. Therefore, final model used for this study is Negative Binomial Regression model. Model diagnosis was done using log likelihood and it is presented on the **Table 5.**

Table 5 A Model comparison criterion's from all extension of count data model for frequency of seizure and associated factors in University of Gondar Referral Hospital, 2017.

Model	Log likelihood
Poisson regression	-475.7
Negative binomial	-474.3

In the bivariable analysis most variables like age, sex, marital status, occupation, educational status, wealth index, smoking, alcohol, chat, strenuous exercise, sleep deprivation, sleeping hours, head injury, treatment side effect, current medication, treatment modality, adherence, duration of treatment, humidity, flickering light and noise became significant with p value< 0.2 and taken for multivariable analysis. In multivariable analysis from the above listed variable only education status (college/university), wealth index, sleep deprivation, adherence, duration of treatment (1-5 years), noise and flickering light are statistically significant with seizure frequency. The table below shows the negative binomial output of those variable statistically significant in multivariable analysis and only those which are significant in bivariable analysis with p value <0.05.

Table 6 Negative Binomial Poisson Regression model of seizure frequency in the last two months and associated factors among patients with epilepsy in University of Gondar Referral Hospital in 2017 (n=408).

Variables	Seizure frequency/2 months				CIRR(95%CI)	AIRR(95%CI)
	0	1-5	6-10	>10		
Occupation						
Student	80	53	0	0	1	1
Farmer	61	44	5	1	1.75(1.13-2.7)	1.439(0.81-2.39)
Merchant	22	11	0	0	0.99(0.53-1.87)	1.21 (0.64-2.27)
Employee	24	20	1	0	1.19(0.72-1.98)	1.27 (0.73-2.20)
Housewife	37	10	2	1	0.34(0.64-2.8)	1.46(0.77-2.75)
Other	18	18	0	0	1.6(1-2.57)	1.26(0.69-2.30)
Educational status						
No formal education	93	59	6	0	1	1
Primary	61	55	1	1	1.01(0.67-1.51)	1.11(0.70-1.74)
Secondary	54	23	1	1	0.84(0.46-1.53)	0.83 (0.47-1.47)
College /university	34	19	0	0	0.56(0.33-0.95)	**0.48(0.24-0.95)***
Marital status						
Single	130	97	4	2	1	1
Married	90	44	4	0	0.75(0.5-1.11)	0.70(0.49-1.00)
Divorced	14	4	0	0	0.85(0.51-1.43)	0.86 (0.45-1.64)
Widowed	8	0	0	0	0.64(0.2-2)	0.59(0.21-1.63)
Wealth index						
Poor	70	75	7	1	1	1
Middle	100	44	1	1	0.48(0.3-0.74)	**0.65(0.46-0.91)***
Rich	72	37	0	0	0.42(0.28-0.62)	**0.55(0.38-0.8)****
Strenuous exercise						
No	222	133	5	1	1	1
Yes	20	23	3	1	1.8(1.07-3.02)	0.96 (0.63-1.47)
Sleep deprivation						

No	216	113	6	0	1	1
Yes	26	43	2	2	2.22(1.46-3.4)	**1.63(1.14-2.34)***
Head injury						
No	238	143	7	1	1	1
Yes	3	12	1	1	3.5(1.9-6.4)	1.45(0.82-2.57)
Adherence						
Low	23	71	4	2	1	1
Moderate	72	52	3	0	0.47(0.32-0.7)	**0.57(0.40-0.80)***
High	146	33	1	0	0.21(0.13-0.33)	**0.28 (0.19-0.41)*****
Duration of Rx						
< 1year	24	28	0	0	1	1
1-5 year	136	63	4	1	0.63(0.42-0.96)	**0.55(0.35-0.86)***
5-10 year	51	45	2	0	0.8(0.52-1.23)	0.73(0.46-1.17)
>10 year	31	20	2	1	1.15(0.63-2.1)	0.75(0.44-1.30)
Light						
No	208	108	3	1	1	1
Yes	34	48	5	1	2.32(1.6-3.37)	**1.58(1.14-2.19)***
Noise						
No	169	80	1	0	1	1
Yes	73	76	7	2	2.89(2.09-4)	**1.7(1.26-2.30)*****

NB: p-value < 0.05= *, < 0.001= ** and 0.000= ***

In the multivariable analysis from the socio economic and demographic factors only educational status and wealth index were statistically significant. The incidence rate of seizure attack was decreased by 52% (AIRR 0.48 and 95%CI 0.24-0.95) among college /university level of education as compared to those who did not attend formal education. The incidence rate of seizure attack in middle economic status was decreased by 35% (AIRR 0.65 and 95%CI 0.46-0.91) similarly; the incidence rate of seizure attack among rich was decreased by 45% (AIRR 0.55 and 95%CI 0.38-0.8) as compared to low economic status.

The incidence rate of seizure attack among those who have experienced sleep deprivation in the last two months was increased by 63% (AIRR 1.63 and 95%CI 1.14-2.34).

From treatment related factors adherence and duration of treatment (1-5 years) are statistically significant and the incidence rate of seizure attack in moderate and high adherence was decreased by 43% and 72% respectively as compared to low adherence. The incidence rate of seizure attack among those took anti-epileptic drug for 1-5 years decreased by 45% (AIRR 0.55 and 95%CI **0.35-0.86**) as compared to those who took for less than one year.

In the group of environment related factors only flickering light and noise became statistically significant and the incidence rate of seizure attack among those who are reported flickering light as provoking factors increased by 58% as compared to those who do not. And, the same association was found between noise and seizure attack which is the incidence rate of seizure attack among those who report noise as a precipitating factors were increased by 70% as compared to those who do not report.

5. Discussion

This study tried to determine the presence and frequency of seizure attacks among patients with epilepsy on follow up at University of Gondar Referral Hospital and the factors associated with seizure. The number of seizure attack in the last two months was reported by 166(40.7%) of the participants with a minimum of 1 and a maximum of 17attacks. Marital status (married), wealth index, sleep deprivation, adherence, and duration of treatment (1-5 year), flickering light and noise became statistically significant factors for seizure attack.

The finding of this study regarding the proportion of study participants who reported number of seizure is lower than another study which found ten or more seizures in the last month prior to the interview in over 50% of the study participants(29). This may be due to small sample size used by the other study (n=100).

Level of education was significantly associated with epilepsy and patient with epilepsy is much more likely to be illiterate and less likely to complete higher education(30). This study found that patient with epilepsy who attends higher education (college/ university) was less likely to experience seizure attack as compared to those who did not attend formal education. The incidence rate of seizure attack among the economic status PWE had a negative statistically significant association with frequency of seizure. In this study the incidence rate of seizure was lower among middle class and rich respondents as compared to those who are poor.

This study found a positive statistical significant association between sleep deprivation and seizure attack. Respondents who reported sleep deprivation in the last two months had a higher incidence rate of seizure attack as compared to those who do not report. A multi center study conducted in Denmark, Norway and United states also found positive association between sleep deprivation and seizure attack. According to the multi center study, patients with generalized epilepsy were found to be highly sensitive to sleep deprivation and seizure attack. (31). The possible reason could be majority of the respondents in the present study diagnosed by epilepsy were with generalized seizure type. The baseline assessment of a controlled prospective study also found higher seizure frequency in sleep deprived group. However, the same study showed no statistically significant association between sleep deprivation and seizure attack during

follow up(32). This may be because the study was limited to patients with refractory epilepsy and the participants did not consume any illicit drug. However, in the present study there were respondents who consume alcohol, cigarette and chat. The other possible reason might be a small sample size used in the other study (n=86).

The ultimate goal of treating epileptic patients is to reduce seizure to the minimum preferably to zero. Duration of treatment plays a great role for effective control of seizure. This study found that the incidence rate of seizure was lower among patients who have been taking AED for 1-5 years as compared to those who took AED for <1 year. This study is also consistent with an institution based cross- sectional study conducted in Uganda which shows a negative statistically significant association between seizure attack and duration of treatment (23). However the present study shows statistically significant association between seizure frequency and taking treatment for only 1-5 years duration. This may be due to difference on the inclusion criteria of the study participants included respondents were those who took AED for more than 6 months.

On the basis of 8 item MMAS about 75.24% of the study participants were non adherent to anti-epileptic treatment. This is higher than the finding of another study which also found non adherence to treatment on the majority (64%) of study participants(33). This may be due to difference in sample size and convenience sampling techniques used in the other study. This study also found respondents who were adherent to their AED treatment had lower risk of seizure attack as compare to non adherent. This study finding is in line with a retrospective study and a cross sectional studies which found statistically significant association between the higher risk of seizure and non adherence to AED(23, 34). Non adherence to AED and seizure are frequently associated variables as reported by different studies. A pilot survey on the relationship between poor medication adherence and seizures also found a statistically significant association between missing dose of a medication and higher risk of seizure attack(35). However, this study is not consistent with prospective seizure diary study which revealed no statistically significant association between non adherence and seizure frequency even in univariable analysis of the study(36). This may be due to difference in the measurement of medication adherence, difference in

participants demographic characteristics (age) and difference on the inclusion criteria. The other study only include patient with diagnosed with localized type of seizure. However, in the present study majority of the respondents were diagnosed by epilepsy with generalized type of seizure.

Environmental factors like light and noise have positive statistical association with epileptic seizure attack. Study participants who report light as a seizure precipitant had a higher risk of experiencing seizure. A prospective study with large sample size shows a significant association between light and seizure attack. In the same study patients with generalized epilepsy were found to be highly sensitive to flickering light than those with localization related epilepsy(31). This consistency may be due to in the present study majority of the patients with epilepsy were diagnosed by epilepsy with generalized seizure type. However, study conducted in London showed that light is not statistically significantly associated with seizure frequency(16). Again this finding is not supported by another study which shows no statistical association between seizure and flickering light(23). This may be due to small sample size (n=104) and difference along with different models applied for the analysis of factors. The incidence rate of seizure attack is higher among respondents who reported noise as a seizure precipitant factor as compared to those who do not report.

This study has an implication for improvement in health care practice of health professional while providing care for patient with epilepsy including improvement on communication between health professionals and patient with epilepsy. The other implication of this study goes to decision makers to consider epilepsy care related program and policy. This study also indicates the need for future prospective study.

6. Limitation and strength of the study

Strength

The strength of this study is addressing seizure frequency as a count outcome variable with the application of advanced statistical model for better estimation of seizure frequency and associated factors. The other strength of this study is the exposure time (2 months) used in this study believed to reduce recall bias on the report of number of seizure attack.

Limitation

The main limitation of this study is the finding may not be generalizable for patients with epilepsy outside the study area. The second limitation of this study is the use of cross sectional design so; it is difficult to show the temporal relationship of the outcome and predictors. This problem needs to be addressed by further multi centered prospective studies.

7. Conclusion

In this study seizure attack were reported by 40.7% of the study participants with a minimum of 1 and a maximum of 17 seizure/2months. This figure is higher from the expected seizure frequency which is preferably zero. Educational status (college/university), wealth index (middle and rich), sleep deprivation, adherence, duration of treatment (1-5 years), flickering light and noise are found to be independent predictors of number of seizure attack.

8. Recommendations

Based on the finding of this study the following recommendations are forwarded:

To government

- Cost of treatment may be a contributing factor for non adherence so providing free health services for patients with epilepsy would minimize the problem.
- Providing especial support and opportunity for patient with epilepsy in higher education program.

To health professional

- For effective control of seizure, it would be better if a health professional puts a great effort on increases awareness on the importance of adhering to antiepileptic treatment for predetermined duration.
- Close communication between health professionals and epileptic patient would be important to identify self perceived seizure triggering factors.
- Health information dissemination for patient with epilepsy about common seizure provoking factors and control mechanism.
- Providing insight about the importance of having seizure diary for effective control of seizure attack by increasing self perception to seizure provoking factors.

To community and family members

- Family and community members' attention and support plays a great role for patient with epilepsy to increase adherence as well as to prevent health related and social consequences by avoiding and/or reducing seizure provoking factors like flickering light and noise.

To researchers:

- For a problem like epilepsy, multi center prospective study would better estimate the association as well as the temporal relationship of different determinant factors and seizure. This question would be answer if researcher considered conducting such kinds of studies.

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Annexes

Annex-1: Information sheet

Title: Frequency of seizure in the last 2 month and associated factors among patient with epilepsy aged above 15 years in University of Gondar Referral Hospital, 2017.

Name of principal investigator: Mekdes Tigistu

Name of Advisors: Dr. Telake A (MSc, Ph.D.) and Mr. Adisu J (MPH)

Name of organization: University of Gondar, College of Medical and Health Science, Institute of Public Health

Name of Sponsor: Gondar University

Introduction: This information sheet is prepared with the aim of explaining about the research project that you are asked to join and provide appropriate information by the group of research investigators. The research group includes one main principal investigator, seven trained data collectors, two supervisors and two advisors from University of Gondar.

Purpose of the study

The purpose of the study is to determine frequency of epileptic seizure in the last 2 month and associated factors among patient with epilepsy aged above 15 years in University of Gondar Referral Hospital, 2017.

Procedure

The study mainly uses data from participant interview and from medical review chart. Permission was obtained from University of Gondar Referral Hospital and study participants.

Risk and benefit

You will not face any harm or discomfort and experience any risk by participating in this research project except your time (30 minutes). There will not be any incentive provided for you but there will be feedback or the study finding will be disseminated for

the purpose of improving the health status of all patients with epilepsy and program modification for better care provision.

Confidentiality

Personal identifier like your name will not be necessary besides the information collected will kept confidentially and it will be documented and stored in a file and it will not be accessed by anyone except the principal investigator.

Person to contact

This research project was reviewed and approved by the Ethical Clearance Committee of University of Gondar institutional review board. If you have any questions or concerns about this study please contact the following individuals:-

1. Mekdes Tigistu: phone no: 0930859630, Email; mekdestigistu10@yahoo.com
2. Dr. Telake A : phone no:0918771951, Email: atelake07@gmail.com
3. Mr. Adisu J: phone no: 0945014569, Email: adeyjem@gmail.com

Annex-2: Informed consent

Hello! My name is …… and I am a nurse. We are interviewing patient with epilepsy who came for follow-up. You are selected randomly and we are requesting you to answer the question that we have prepared for you. The purpose of the study is to assess epileptic seizure frequency in the last 2 months and associated factors among patient with epilepsy aged above 15 years, whether they experience seizure or not. This research will be beneficial for all epileptic patients so we will ask you a series of question that may take 30 minutes. You name and other personal identifiers are not necessary so your answer kept confidentially. You can refuse to respond any part of the study question or you can stop at any point in the interview.

Do you agree to participate in the study?

A. Yes……continue with the interview
B. No ……...go to the next participant

Thank you for being voluntary to participate in the study. I have been briefly informed about the study and I clearly understood the objective. Consequently, I hereby approve my consent to take part in the study as an Interviewee with my signature

Signature_____ Date_____

Name and Signature of interviewer

Name, _____ Signature_____ Date_____

Supervisor

Identification number of respondent_____

Start time; _____

Annex-3: Assent form

Greeting

Hello! My name is …… and I am a nurse. We are interviewing patient with epilepsy who came for follow-up. Your child is selected randomly and we are requesting if you are volunteer we will be very grateful. The purpose of the study is to assess epileptic seizure frequency in the last 2 months and associated factors among patient with epilepsy aged above 15 years, whether they experience seizure or not. This research will be beneficial for all patient with epilepsy so we will ask you a series of question that may take 30 minutes. Your child name and other personal identifiers are not necessary so your answer kept confidentially. You can refuse to respond any part of the study question or you can stop at any point in the interview.

May I continue?

A. Yes, continue the interview
B. No, proceed to the next patient

Thank you for being voluntary to participate in the study.

I have been briefly informed about the study and I clearly understood the objective. Consequently, I hereby approve my assent for my child to take part in the study as an Interviewee with my signature

Signature_____ Date_____

Name and Signature of interviewer

Name, _____ Signature_____ Date_____

Supervisor

Name, _____ Signature_____ Date_____

Identification number of respondent (card number)_____

Start time; _____

Annex-4: Questionnaires

Date _____

ID: _____

Number of seizure attack in the last three months_____

Q. No	Variable	Labels Card number: _____
	I. Socio economic variables	
1.	Age	_____(years)
2.	Sex	I. Male II. Female
3.	Marital status	I. Single II. Divorce II. Married IV. Widowed
4.	Occupation	I. Student II. Farmer III. Merchant IV. Government and non government employee V. Other
5.	Educational status	I. Illiterate II. Secondary III. Primary IV. College/University
6.	Residence	I. Urban II. Rural
II.	**III. Behavioral factor**	
7.	Did you smoke cigarette? (history of smoking in the last 2 months)	I. Yes II. No
8.	Did you consume alcohol? (history of alcohol consumption in the last 2 months)	I. Yes II. No
9.	Did you chew Chat? (history of chewing chat in the last 2 months)	I. Yes II. No
10.	Have you engaged in strenuous exercise in the last 2 months?	I. Yes II. No
11.	Common emotional response to stressors	I. Anger II. Frustration III. Worry IV. Anxiety
12.	Have you suffer for sleep deprivation for the last 2 months?	I. Yes II. No
13	How many hours/day did you sleep?	_____hours
14.	Did you feed your meal on time?	I. Yes II. No
	Clinical factor	

15.	Did you suffer from any head injury in the last 2 months?	I. Yes II. No
16.	Have you been treated for any disease for the last two months?	I. Yes II. No
17.	If yes to question number 23 what was the diseases?	I. Acute febrile illness (Malaria, Typhoid, Pneumonia, meningitis, upper respiratory tract infection…) II. Parasitic infection III. Other(specify)_____
IV.	**Treatment related**	
18.	Date of treatment started?	_____DD/MM/YY
19.	For how long you took AED?	_____(years)
20.	Type of drug when treatment started?	I. Phenobarbital II. Carbamezapine III. Phentoyin IV. Other (specify
21.	Date of first tapering?	_____ DD/MM/YY
22.	The number of AED that you are taking?(treatment modality)	I. Monotheraphy II. Polytheraphy
23.	What is the current medication you are taking?	II. Phenobarbital III. Carbamezapine III. Phentoyin IV. Other (specify)
24.	What was the dose of your medication before two months?	_____mg
25.	Is there any tapering of the dose in the last two months?	I. Yes II. No
26.	What is the current dose of your medication?	_____mg
27.	Is the treatment affordable for you?	I. Yes II. No
28.	Did you experience treatment related side effect?	I. Yes II. No
V.	**Seizure related**	
29.	Have you experience seizure attack in the last two months?	I. Yes II. No
30.	How many seizure attacks did you experience in the last two months?	_____(specify the number)
31.	What was the type of seizure during diagnosis?	I. Partial seizure II. Generalized seizure III. Unclassified seizure

VI.	Environmental factors	
32.	Can humidity provoke seizure attack for you?	I. Yes II. No
33.	Can the flickering light in a place provoke seizure attack for you?	I. Yes II. No
34.	Can noise provoke seizure attack for you?	I. Yes II. No
35.	Can change in weather condition provoke seizure attack for you?	I. Yes II. No

Morisky medication adherence scale

Question	Response
1. Do you sometimes forget to take your anti epileptic medications?	Yes (0) No(1)
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 3 months, were there any days when you did not take your antiepileptic medicine?	Yes (0) No(1)
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?	Yes (0) No(1)
4. When you travel or leave home, do you sometimes forget to bring along your antiepileptic medication?	Yes (0) No(1)
5. Did you take your antiepileptic medicine yesterday?	Yes (0) No(1)
6. When you feel like your epilepsy (seizure) is under control, do you sometimes stop taking your medicine?	Yes(0) No(1)
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your antiepileptic treatment plan?	Yes(0) No(1)
8. How often do you have difficulty remembering to take all your medications?	Never (1), Rarely, sometimes, and always (0).
Total score	

Wealth index

A. For urban residents only

No	Questions	Response	Skip
601	Do you belong to the house?	1. Yes 2. No	
602	What is the roof of the main house?	1. Corrugated iron sheet 2. Thatch 3. Other specify ----------	
603	What is the wall of the main house?	1. Mud 2. Cement 3. Bricks 4. Other specify --------	
604	What is the floor of the main house?	1. Soil 2. Cement 3. Ceramic 4. Other specify ----------	
605	Availability of electricity	1. Yes 2. No	
606	Availability of radio	1. Yes 2. No	
607	Availability of television	1. Yes 2. No	
608	Availability mobile	1. Yes 2. No	
609	Availability of non-mobile telephone	1. Yes 2. No	
610	Availability of refrigerator	1. Yes 2. No	
611	Availability of chair	1. Yes 2. No	
612	Availability of table	1. Yes 2. No	
613	Availability of bed with cotton/sponge/spring matters	1. Yes 2. No	
614	Availability of electric baking stove	1. Yes 2. No	

	B. For rural residents only		Skip
615	Do you belong to the house?	1. Yes II. No	
616	Type of the house	1. Corrugated iron sheet 2. Thatch 3. Other specify ----------	
617	Availability of radio	2. Yes 2. No	
618	Availability of mobile telephone	3. Yes 2. No	
619	Availability of table	4. Yes 2. No	
620	Availability of chair	5. Yes 2. No	
621	Availability of bed with cotton/ sponge/spring matters	6. Yes 2. No	
622	Availability of electricity	7. Yes 2. No	
623	Availability of kerosene lamp/pressure lamp	8. Yes 2. No	
624	Does the household own any agricultural land?	9. Yes 2. No	
625	How many (local units) of agricultural land do you own?	1. Private ---------- (local unit) 2. Rent ---------- (local units)	
	Annual farm product per quintal		
626	Teff	---------- quintal	
627	Barley	---------- quintal	
628	Maize	---------- quintal	
629	Rise	---------- quintal	
630	Wheat	---------- quintal	
631	Sorghum	---------- quintal	
632	Bean	---------- quintal	
633	Pea	---------- quintal	
634	Chickpea	---------- quintal	
	Availability of cattle's		
635	**How money of the following animal does the household own?**		
636	Milk cows, oxen or bulls	---------- in number	
637	Back animals (Horses, donkeys, or mules)	---------- in number	
638	Goats?	---------- in number	
639	Sheep?	---------- in number	
640	Chickens?	---------- in number	
641	Beehives?	---------- in number	

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14.	□□□□ □□□□ □□□□ □□ □□□□□□?	I. □□ II. □□□□□	
I. □□□□□			
15.	□□□□ 2 □□□ □□□ □□□□□ □□ □□□□ □□□ □□□?	I. □□ II. □□□□□□□	
16.	□□□□ 2 □□□ □□□ □□□□□□ □□□ □□□□ □□□□?	I. □□ II. □□□□□	
17.	□□□□ □□ □□□ 20 □□□□ □□ □□□ □□□□□ □□□ □□?	I. □□□□□□ □□□□ □□□□□ (□□□□□□□□□□□□□□□□, □□□□□□□□□□□□□□ □□□□□ □□□□ □□□□…) II. □□□□□ □□□□(Parasitic infection) III. □□ (□□□□)_____	
IV. □□□□□□□□□□□□			
18.	□□ □□ □□□□□ □□□□□?	_____□□/□□/□□□	
19.	□□□□□□ □□□□□ □□□□□ □□□□ □□□□□ □□?	I. Phenobarbital II. Phentoyin III. Carbamezapine IV. □□ (□□□□)_____	

20.	□□□-□□□□ □□□ □□□□□□ □□□ □□□ □□ □□□□□?	_____(□□□)	
21.	□□□□□□ □□□□□□ □□□?	I. □□□-□□□□ (□□□ □□□) II. □□□-□□□□	
22.	□□□ □□□□□ □□□ □□□□□□ □□□□ □□□□ □□?	I. Phenobarbital II. Phentoyin III. Carbamezapine IV. □□ (□□□□)_____	
23.	□ □□□ □□□ □□□ □□□□ □□□□□ □□□□□□ □□□ □□□ □□□?	_____ □□.	
24.	□□□□ □□□□□ □□□□□□ □□□ □□ □□□□ □□□ □□□ □□□ □□□ □□□□□ ?	I. □□ II. □□□□□□	
25.	□□□ □□□□□□ □□□□□□ □□□ □□ □□□ □□?	_____ □□.	
26.	□□□□□□ □□ □□□□ □□□□□ □□?	I. □□ II. □□□□□	
27.	□□□□□□ □□□□□ □□ □□□□ □□□□□ □□□□□ □□□□□ □□□ □□?	I. □□ II. □□□□□	
V.	□ **Seizure** □□□□□		
28.	□□□□ 2 □□□ □□□ □□□□/ □□□□□□ □□□□ □□□□□□□?	I. □□ II. □□□□□□□	
29.	□□□□ 2 □□□ □□□ □□ □□□□/ □□□□□□ □□□□ □□□ □□ □□□□□□□?	_____(□□□□□□□□)	
30.	□□□ □□□□/□□□□□□ □□□□ □□ □□□?	I. □□□ □□□□□□ II. □□□□□ □□□□□□ III. □□□□□□(unclassified)	
31.	□□□ □□□□□□ □□□□ □□□□ □□□□□□□ □□ □□ □□□?	_____ _____	
VI.	□□□□□ □□ □□□□□		
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33.	□□□□□ □□□ □□□□□□□ □□□□ □□□□□□□ □□□□?	I. □□ II. □□□□□□□□□	
34.	□□□ □□□□□□□ □□□□ □□□□□□□ □□□□?	I. □□ II. □□□□□□□□□	
35.	□□□□ □□□ □□□□□ □□□□□□□ □□□□ □□□□□□□ □□□□?	I. □□ II. □□□□□□□□□	
Morisky□□□□□□□□□ □□□			
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2.	□□□ □□□□□ □□ □□□□□ □□ □□□□ □□□□□□ □□□□□□□ □□□□□ □□□□□□□□□ □□□ □□□ □□□ □□□□□□ □□-□□□□ □□□ □□□□□ □□□□□ □□□□□□ □□ □□□□□□ ?	□□ (0) □□□□□□□ (1)	
3.	□□□□□□ □□□□ □□ □□□□ □□□ □□□□□□□ □□ □□□□□ □□□□□ □□□□□□ □□□□ □□□□□	□□ (0) □□□□□(1)	

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5.	□□□□ □□□□□□ □□-□□□□ □□□ □□□□□ □□□□ □□□?	□□ (0) □□□□□□ (1)	
6.	□□□□□ □□□□ (seizure) □□□□□□□□□ □□□□□□□□□□ □□ □□□□□□ □□□□□ □□□□ □□□□?	□□ (0) □□□□□ (1)	
7.	□□□□ □□□□□ □□□□ □□□□□□ □□□ □□□ □□ □□□□□□ □□□ □□□ □□-□□□□ □□□ □□□□□□ □□□□□ □□□□□□ □□□□□□ □□□ □□□□□ □□□□?	□□ (0) □□ (1)	
8.	□□ □□□ □□□□□ □□□□□ □□□□□□□ □□□ □□□□?	□□□□ (1), □□□□□□, □□ □□□□ (0).	
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3.	□□□ □□ □□□□ □□□□ □□?	1. □□ 2. □□□□ 3. □□ 4. □□□□□□□ --------	
4.	□□□ □□ □□□ □□□□ □□?	1. □□□ 2. □□□□ 3. □□□□ 4. □□□□□□□ ----------	
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24.	□□□□□ □□□□ □□□ □□□□ □□ □□?	1. □□ 2. □□□	
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